Introduction

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The renin-angiotensin system was discovered by Tigerstedt and Bergman in 1898. For a long time it remained in the domain of esoteric experimentation, largely in the realms of hypertension and endocrinology. It seems almost incredible that, until the availability of angiotensin converting enzyme (ACE) inhibitors in the 1980s, the importance of this vital neuroendocrine system was recognised by only a minority of the medical community. Until recently, the cynical observation that there were many more people living off the renin-angiotensin system than dying because of its malfunction, was widely, if tacitly, accepted.

Such unpropitious antecedents make the recent spectacular rise in medical interest in the system and its therapeutic manipulation a minor miracle. As recently as 1976, a respected authority, Franz Gross wrote, "Undoubtedly, the antagonists and inhibitors of the renin-angiotensin system are most useful tools, but their application will be limited to the share of renin-dependent forms of high blood pressure in the total field of hypertension". Within a few years this prophecy was dramatically discredited. Antagonists of the renin-angiotensin system, introduced into therapeutics in the 1980s, have revolutionised understanding of this neuroendocrine system and treatment of two of the most important cardiovascular problems of the developed world, namely, hypertension and heart failure.

Classical and contemporary views on the renin-angiotensin system

The classical view of the renin-angiotensin system was that of an endocrine system acting via an effector hormone, angiotensin II, which was responsible for all the observed physiological effects. Angiotensin II acted on specific receptors on the cell membrane, but the system was essentially dependent on the circulating hormone to produce all its physiological consequences. With the availability of tools with which to block the renin-angiotensin system at multiple sites in the 1980s this traditional view underwent radical change. Through the research of Dzau, Ganten, Unger, Lindpainter, and others it was convincingly shown that all essential elements of the renin-angiotensin system are present in a variety of tissues. Thus angiotensin II can be generated in situ, in the vascular wall, and the ventricular myocardium. These observations extended the potential role of this system from a pure endocrine role to paracrine and autocrine roles in cardiovascular homeostasis. The precise importance of the "tissue" as opposed to the "circulating" renin-angiotensin system in the genesis of cardiac and vascular pathophysiological states is still debated, but its existence is no longer in doubt.

Even more recent advances in molecular biology of this system have shown that in the generation of angiotensin II from angiotensinogen, the classical renin-converting enzyme pathway is not the sole route for angiotensin II production. In certain situations, notably severe heart failure, especially when treated with ACE inhibitors, angiotensin II may be generated by local tissue enzymes such as chymases. The pathophysiological importance of this alternative pathway is as yet to be fully worked out.

There have been major advances in our understanding of the angiotensin II receptor. It is now clear that there are several subtypes. In humans, the predominant one is the AT_1 subtype, which is responsible for virtually all the observed effects of angiotensin II in man. It is a conventional G protein coupled receptor with cyclic guanosine monophosphate (cGMP) as the second messenger. There is also at least one other human subtype, the AT_2 receptor, the function of which is as yet incompletely understood. It may mediate much of the growth promoting effects of angiotensin II. Other angiotensin II receptor subtypes have been identified in other species. This appears to be another area set for explosive scientific and therapeutic growth with the availability of specific non-peptide receptor antagonists.

The heart and the renin-angiotensin system

Although the renin-angiotensin system is ubiquitous, much of the scientific and therapeutic endeavour has focused on the heart. Up to 1995 there had been around 2000 references devoted to this aspect of the system. Interactions between the heart and the renin-angiotensin-aldosterone system have become an important theme in contemporary cardiology. Initially, the major topic of interest was the effects of renin-angiotensin system on the heart, as a direct result of systemic hypertension. A frequent outcome of this interaction was heart failure; hence much of the early work on the renin-angiotensin system and heart failure focused on reduction in left ventricular afterload by lowering blood pressure. The next breakthrough was the discovery that not only did hypertensive heart failure respond to inhibition of the renin-angiotensin system, but so too did cardiac failure in nor-

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motensive individuals, where the symptoms responded most satisfactorily.

A major advance in therapeutics was the finding that not only symptoms, but also survival, was improved by interruption of the renin-angiotensin system. The first ever randomised, double blind therapeutic trial to show prolonged survival with a therapeutic intervention was the CONSENSUS-1 trial, where the ACE inhibitor enalapril or placebo was given to severely incapacitated individuals. This trial clearly showed that the administration of enalapril in addition to conventional treatment with digitalis, diuretics, and other vasodilators resulted in improved survival.

Further trials over the next decade clearly established that the administration of ACE inhibitors to patients early in the evolution of heart failure improved survival by delaying the development of overt heart failure, reducing symptoms and periods of hospital admission, with enormous clinical and economic advantages to patients and society.

Most recently, inhibition of the renin-angiotensin system has been tested in patients suffering from acute myocardial infarction. The seminal work of Janice and Marc Pfeffer in the rat model of post-myocardial infarction heart failure developed the concept of the process of "ventricular remodelling", where changes in left ventricular geometry and structure as a consequence of infarction set in train a cascade of haemodynamic and neuroendocrine changes which progress to florid heart failure. This concept was subsequently extended to other aetiologies of heart failure, the unifying factor which initiated the process being an increase in wall stress. In short, once there was an increase in wall stress, whatever its cause, progression to frank heart failure was due to the generic response of the heart to this increased wall stress, irrespective of the specific attributes of particular aetiological agents. The Pfeffers also showed that the remodelling process could be attenuated and survival improved by ACE inhibitors. This led to small, focused, post-infarction studies on left ventricular function by Pfeffer and Sharpe, together with their colleagues, which provided clinical confirmation of experimental observations. The final piece of the jigsaw was the demonstration in massive randomised trials, notably the survival and ventricular enlargement (SAVE), and acute infarction ramipril evaluation (AIRE), and trandolapril cardiac evaluation (TRACE) trials, that symptoms and survival are improved by ACE inhibitor treatment initiated within a few days of the onset of acute myocardial infarction. The evidence from post-acute myocardial infarction trials shows unequivocally that the mortality and morbidity from subsequent heart failure is improved if these drugs are given a few days after the onset of infarction to individuals with evidence of impaired cardiac function but no florid heart failure.

There are data which show that even earlier administration of ACE inhibitors within 24 hours of the onset of acute infarction conveys additional benefit above and beyond that of other treatment, including thrombolysis. Studies such as the captopril and thrombolysis (CATS), ISIS-4, GISSI-3, SMILE, and PRACTICAL all show improvement in surrogate or real end points of morbidity and mortality in acute myocardial infarction patients, beyond that due to all other conventional treatments.

Studies are in progress as to the optimal timing, dosage, and duration of ACE inhibition following acute infarction. We are also in the throes of establishing which type of patient benefits most from such treatment. Available evidence suggests that the benefits in heart failure and myocardial infarction are almost certainly common to all members of the class. Randomised, head to head comparisons are few. One study, PRACTICAL, which compared the effects of captopril and enalapril on post-myocardial infarction ventricular remodelling, showed that the drugs had very similar effects. There is good evidence that the benefits on survival are a particular attribute of ACE inhibition not shared by other vasodilator drugs. The second Veterans heart failure (V-HeFT II) trial showed that enalapril was superior to the combination of isosorbide dinitrate and hydralazine as regards improved survival.

The major focus of research in hypertensive heart disease has shifted from merely lowering the blood pressure, which these drugs do remarkably effectively even in so called refractory hypertension, to regression of left ventricular hypertrophy, to reducing what has become recognised as a major, independent cardiovascular risk factor.

Such investigations have led to the examination of angiotensin II as not just a hormone, but also as a growth promoting factor at the cellular level. There is an impressive body of data confirming that structural alterations in left ventricular and vascular walls, referred to as "remodelling" are, in some measure, mediated by angiotensin.

Pari passu with therapeutic advances have been advances in understanding of the basic physiology of the renin-angiotensin-aldosterone system as it affects the heart. The classical paradigm of angiotensin II was that of a highly potent vasoconstrictor substance acting predominantly on the systemic arteries and veins, and its role in salt and water physiology. Then it was found to interact and modify the actions of the sympathetic system. Further research led to discovery of its cellular growth promoting actions. Its role in the pathology of left ventricular hypertrophy became increasingly appreciated as well as the realisation that the regression of left ventricular hypertrophy was a desirable end point of medical therapy.

Genetics of the renin-angiotensin system and the heart

Research has now shifted to molecular biology of the renin-angiotensin system. The discovery by Cambien and associates that insertion/deletion polymorphism of the ACE gene

is associated with a higher risk of developing myocardial infarction is one report that relates to Alderman's finding that high circulating renin concentrations correlate with a higher risk of heart attacks in a hypertensive population. These observations on the genetics of the renin-angiotensin system as a risk marker for myocardial infarction have been extended to the angiotensin II receptor gene and the angiotensinogen 458 gene, providing some other evidence for interrelations between the heart and the renin-angiotensin system. However, some (for example, Harrap) are *very* cautious about the intimacy of this relation. This really is a complex and confusing field at present!

The success of therapeutic endeavour in the area of renin-angiotensin system blockade is all the more remarkable for the extreme paucity of undesirable side effects. Whilst non-specific effects of an allergic nature are present infrequently, the only real side effect which has proved troublesome in clinical usage has been the ACE inhibitor cough. This side effect occurs in approximately 5–8% of European subjects and at a somewhat greater frequency in non-Europeans. It is sufficiently frequent to jeopardise widespread use of ACE inhibitors. This can be avoided by blocking the renin-angiotensin system more specifically at a point either proximally or further down in the cascade. Thus renin inhibitors and angiotensin II receptor blocking drugs both produce similar cardiovascular effects to converting enzyme blockade without elevation of kinins or prostaglandins. These agents have been shown to lower blood pressure satisfactorily without inducing cough.

Renin inhibitors, theoretically, are attractive alternatives to ACE inhibitors as they should have all the desirable features of angiotensin blockade without the additional features of increased prostaglandin and bradykinin levels. They have been successfully used in experimental models of heart failure and hypertension. Unfortunately, their clinical use has been bedevilled by problems. It is, therefore, unlikely that renin inhibitors will enter the therapeutic arena in the foreseeable future.

Angiotensin II AT_1 receptor blocking drugs, on the other hand, appear therapeutically to be much more promising. Initial attempts to block the angiotensin II receptor used peptide drugs such as saralasin. These required parenteral administration, had significant agonist action, were subtype non-specific, and were therefore unsuited for therapeutic use. Intensive research by several groups of workers in the pharmaceutical industry led to the synthesis of non-peptide compounds capable of blocking the angiotensin II AT_1 receptor. Losartan is one such non-peptide receptor antagonist which competitively blocks this receptor site. It is the agent which has been studied most in the clinical context and is currently licensed for clinical use in hypertension in Europe. Early clinical trials in hypertension and heart failure clearly show its efficacy in reducing blood pressure and relieving heart failure symptoms. The exact place of these agents vis-a-vis converting enzyme inhibitors in treatment of cardiac diseases remains to be established by appropriate clinical trials.

The renin-angiotensin system and cardiac arrhythmias

Receptors for angiotensin II are present in the specialised conducting tissue, but their precise function remains to be established. Experimental studies show that blockade of the renin-angiotensin system before or shortly after induction of an acute myocardial infarct protects against the development of ventricular fibrillation. In patients with chronic heart failure the frequency and complexity of ventricular premature beats are significantly reduced according to most studies. However, most of the mega trials of converting enzyme inhibitor therapy in chronic heart failure have not shown a reduction in sudden, presumably arrhythmic, cardiac deaths. The reasons for this lack of significant protection against sudden death are unknown.

Conclusions

The past two decades have seen an explosive growth in knowledge concerning the renin-angiotensin system and the heart. This has been converted into therapeutic benefits both for treating and delaying disability and death from hypertension and heart failure. There have been substantial economic and social benefits from widespread use of agents designed to interrupt this system. Regrettably, despite intensive efforts at education of the medical community by scientists, clinicians, and the pharmaceutical industry, much conservatism in the proper use of ACE inhibitors is still widespread. For example, a recent audit from Britain showed that only 40% of heart failure patients had been given ACE inhibitors. Similar results have been reported from the United States and other advanced countries which should have been well informed as to the appropriate treatment of this condition. It has been shown that cardiologists are most likely to prescribe ACE inhibitors appropriately for heart failure, whereas primary care physicians are least likely, with internists in between. Therefore, there still remains a great deal of education to be done and this Supplement is one such attempt. Our objective is the same as a symposium held in Venice in the early 1980s, when interest in the cardiovascular actions of the renin-angiotensin system was beginning. The aim of that symposium was to collect the leading workers in the field, basic scientists and clinicians, to gather their views on the current situation in their respective fields and their predictions for future directions. The proceedings of that symposium were published as a supplement to *Kidney International*, and formed a standard reference source for several years subsequently.

Today, the sheer number of people engaged in research into the ever increasing areas of scientific and therapeutic importance concern-

ing the renin-angiotensin system precludes any comprehensive meeting on the entire system, let alone assembling them under one roof. Therefore, in recognition of the major scientific and therapeutic place of the research into the cardiac aspects of the renin-angiotensin system, an attempt has been made to replicate the ambitions of the original "Venice Symposium" in this paper symposium. We have invited the leading authorities actively researching various cardiac aspects of the renin-angiotensin system to produce contributions which are intended to be state of the art overviews. It is hoped that this Supplement will, like its predecessor, remain a valuable source of reference, guiding current and future research into the heart and the renin-angiotensin system, for some years to come.